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ORIGINAL ARTICLE

Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers

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Abstract

Objective. Tooth loss has been associated with upper gastrointestinal cancer in several studies, but only one previous study used prospectively collected data. The importance of confounding by *Helicobacter pylori* has not previously been addressed. The objective was to determine the association between tooth loss and upper gastrointestinal cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort and to determine the importance of potentially confounding dietary factors or *H. pylori* seropositivity. ***Material and methods***. A prospective cohort study with 29,124 subjects included 49 esophageal squamous cell carcinomas, 66 esophageal/gastric cardia adenocarcinomas, and 179 gastric non-cardia adenocarcinomas occurring between 1985 and 1999. Cox proportional hazards models adjusted for age and education were used to estimate hazard ratios (HRs) and 95% CIs. Odds ratios and 95% CIs were calculated with and without adjustment for *H. pylori* seropositivity in a nested case-control group to determine whether *H. pylori* confounded the association between tooth loss and gastric cancer. ***Results***. Tooth loss significantly increased the hazard ratio for gastric non-cardia cancer, the HR (95% CI) for edentulous subjects versus those with <10 teeth lost was 1.65 (1.09, 2.49, respectively). No statistically significant associations were found between tooth loss and esophageal squamous cell carcinoma or esophageal/gastric cardia adenocarcinoma. Confounding by dietary factors, tobacco smoking, or *H. pylori* did not explain these results. ***Conclusions***. Tooth loss was associated with increased risk of gastric non-cardia cancer, but not esophageal squamous cell carcinoma or esophageal/gastric cardia adenocarcinoma in this Finnish cohort.

Key Words: *Finland, esophageal cancer, gastric cancer, male smokers, tooth loss*

Introduction

Gastric cancer is the second leading cause of cancer death, world-wide. Risk factors for gastric cancer include age, male gender, diets poor in fruits and vegetables, diets with excessive salt and nitrates, *Helicobacter pylori* infection, and smoking. People with gastric cancer usually have a poor prognosis, so understanding the etiologic factors is particularly important for public health programs that seek to reduce gastric cancer incidence and mortality.

Poor oral health has been associated with increased risk of cancer at several sites. In a number of studies oral cancer has been associated with both tooth loss and poor oral hygiene [1–3]. In some cases this may be related to constant abrasion from dentures that do not fit properly or are not maintained properly. Studies have also examined the effects of tooth loss on cancer of the upper aerodigestive tract below the oral cavity. A case-control study in the People's Republic of China found that regular tooth brushing reduced the risk of esophageal squamous cell carcinoma (ESCC) [4]. An association between oral hygiene and/or tooth loss and gastric cancer has also been reported in retrospective studies conducted in Japan [5], Turkey [6],

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and Germany [7]. A prospective cohort study in China found that tooth loss significantly increased the risk of ESCC, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma [8]. A recent analysis of National Health and Nutrition Examination Survey (NHANES) data suggested that tooth loss may increase the risk of lung cancer [9], but the investigators suggest that confounding by smoking is a concern in the interpretation of that result. Finally, an association between tooth loss and pancreatic cancer was found in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort (ATBC) [10].

In this study, we examine the association between tooth loss and risk of ESCC, esophageal/gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma. In addition, we examine whether numerous dietary factors or *H. pylori* seropositivity confounds the association between tooth loss and gastric cancer.

Material and methods

Subjects, baseline questionnaires, and case ascertainment

The ATBC Trial was a placebo-controlled, double-blinded, 2×2 factorial, primary prevention trial that tested whether α-tocopherol or β-carotene could reduce the incidence of lung cancer in male smokers [11]. Between 1985 and 1988, 29,133 eligible men aged 50–69 years in southwestern Finland who smoked ≥ 5 cigarettes/day were randomly assigned to receive supplements (50 mg α-tocopherol/day, 20 mg β-carotene/day, or both) or placebo. Exclusion criteria from the study included a history of malignancy other than non-melanoma cancer of the skin or carcinoma *in situ*, severe angina on exertion, chronic renal insufficiency, cirrhosis of the liver, chronic alcoholism, current anticoagulant therapy, other medical problems that might limit long-term participation, or current use of supplements containing vitamin E (>20 mg/day), vitamin A ($>20{,}000$ IU/day), or β-carotene (>6 mg/day). The trial ended on 30 April 1993, and follow-up for the present study continued after randomization through April 1999. The study was approved by the institutional review boards of both the US National Cancer Institute and the National Public Health Institute in Finland, and all study participants provided written informed consent before the start of the study. Details of the study rationale, design, and methods have been described elsewhere [11].

At their baseline visit, the study participants completed questionnaires on general background characteristics including self-reported medical, dental, smoking, and dietary history. Dentition was assessed by asking subjects: "How many permanent teeth are you missing: none, 1–5 teeth, 6–10 teeth, >10 but not all teeth, or all teeth?" Diet was assessed by a self-administered dietary history questionnaire, designed and validated specifically for the ATBC study, which determined the frequency of consumption and the usual portion size of >200 food items during the past year, using a booklet with color photographs as a guide for portion size [12]. For 62 subjects with incomplete data on the number of years of smoking, we estimated that variable by subtracting the age at which each subject started smoking from his age at randomization. Height and weight were also measured at baseline.

Cases were identified from the Finnish Cancer Registry, which provides ~100% case ascertainment in Finland [13]. All relevant medical records for reported cases of gastric cancer (ICD9 Code 151) and esophageal cancer (ICD9 Code 150) were reviewed independently by one or two study physicians [14]. The 49 esophageal cancer cases that were diagnosed as squamous cell carcinomas were grouped. The remaining 8 tumors were small cell tumors or not otherwise specified and were excluded. We combined all tumors that infiltrated the esophagogastric junction and two adenocarcinomas above the junction under the rubric esophageal/gastric cardia adenocarcinoma. Finally, the remaining adenocarcinomas in the stomach were grouped and will hereafter be referred to as gastric non-cardia adenocarcinoma. Fifteen gastric cancer cases with histologic diagnoses other than adenocarcinoma were excluded.

H. pylori serologic tests

Fasting serum was collected at the prerandomization baseline visit and stored at -70°C. Frozen baseline serum samples from these subjects were assayed for antibodies to *H. pylori* whole cell and CagA antigen with previously described and validated methods by Dr. Perez-Perez, New York University School of Medicine [15–17]. For the primary analysis, we considered subjects positive for either whole cell or CagA antigen as *H. pylori* positive. Serum from 249 gastric cancer cases and 246 controls were selected for assessment of *H. pylori* seropositivity.

Statistical analysis

Follow-up time for each participant was calculated from the date of randomization until the diagnosis of cancer, death, or April 1999. Only subjects with complete dentition data ($n = 29{,}124$) were included

in all analyses. Generalized linear models adjusted for age were used to estimate means and 95% confidence intervals (CIs) of the cohort characteristics by dentition history for continuous variables to help identify potential confounders. Because disease history variables were categorical, logistic regression was used to estimate age-adjusted proportions and 95% CIs by dentition history. A test for trend was performed for each characteristic across the three tooth loss categories described below. For the trend test we used contrast coefficients based on the midpoint of each dentition category and centered these values on their mean.

Cox proportional hazard models were used to determine hazards ratios (HRs) and 95% CIs. Because the number of cases in which subjects lost no teeth, 1–5 teeth, or 6–10 teeth was low, subjects in these categories were combined for the risk models. Potential confounders were added to the models in a stepwise fashion and were included only if they changed the beta coefficient for tooth loss $\geq 10\%$. The dietary variables used to examine confounding were energy adjusted by the residual method described by Willett & Stampfer [18]; alcohol intake was an exception because it was not strongly correlated to energy. The analyses were initially restricted to subjects with complete dietary data, but, because none of the dietary variables confounded the HR estimates for tooth loss, this restriction was dropped. To examine the impact of *H. pylori* on the risk conferred by tooth loss, we used logistic regression and a nested case-control data set to estimate the odds ratio (OR) and 95% CIs in models with and without variables for *H. pylori* seropositivity. Statistical analyses were performed using SAS, version 8.2 (SAS Institute Inc., Cary, N.C., USA), and Epicure (Hirosoft International Corp., Seattle, Wash., USA). All statistical tests were two-sided with statistical significance set at $p < 0.05$.

Results

The characteristics of the total cohort and cancer cases by site are presented in Table I. Cancer cases tended to be older, have more years of smoking, and greater tooth loss at baseline.

In Table II we present the age-adjusted means and 95% CIs for a number of characteristics and exposures by tooth loss category. A subset of these data has previously been presented, but is repeated here because it is central to some of the risk modeling [10]. In many cases the absolute differences by tooth loss category were small, but all of the factors we examined, with the exception of salt intake, were statistically different by tooth loss category. Tooth loss was associated with lower serum concentrations of α-tocopherol and retinol and lower intakes of alcohol, fruit, starch, zinc, vitamins C and E, and nitrate. Tooth loss was associated with higher intake of nitrite.

Using the analytical cohort and Cox proportional hazards regression, we built parsimonious regression models to estimate the association between tooth loss and the hazard of developing cancer at the three sites, ESCC, esophageal/gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma. Among all the factors presented in Table II, only age and education confounded the association between tooth loss and cancer. Tooth loss significantly increased the hazard ratio for gastric non-cardia adenocarcinoma (Table III), but we found no statistically significant associations between tooth loss and ESCC or esophageal/gastric cardia adenocarcinoma.

We tested different parameterizations of smoking including years of smoking, total number of cigarettes smoked per day, and cumulative pack-years of smoking. Inclusion of any of these three different variables to represent tobacco exposure did not change the beta coefficients for tooth loss (data not shown).

The most important potential confounder for the association between tooth loss and gastric cancer not addressed in Table II and III is *H. pylori* exposure. An analysis of this cohort suggested that *H. pylori* may be marginally associated with tooth loss and is therefore a potential confounder of the tooth loss gastric cancer association [10]. Previously, *H. pylori* status was assessed in a nested gastric cancer case-control subset of the ATBC study (unpublished data). We used this case-control subset to determine whether *H. pylori* status confounded the tooth loss adenocarcinoma association. The adjusted ORs and 95% CIs with and without adjustment for *H. pylori* seropositivity are presented in Table IV. Adjustment for *H. pylori* status had no material impact on the estimates of the associations. This lack of effect was true whether or not we accounted for the presence of CagA positivity (data not shown).

Discussion

In this large prospective study, tooth loss significantly increased the hazard of developing gastric non-cardia adenocarcinoma and this association persisted after adjustment for a large number of potential confounders, including dietary factors, smoking, and *H. pylori* seropositivity. In contrast, tooth loss was not associated with either ESCC or esophageal/gastric cardia adenocarcinoma.

Table I. Baseline characteristics for the overall ATBC Study cohort and among subjects that developed esophageal and gastric cancer between 1985 and 1999.

	Entire cohort[1]	ESCC[2]	Esophageal/gastric cardia adenocarcinoma[3]	Gastric non-cardia adenocarcinoma[4]
N	29,124	49	66	179
Age, mean (SD), years	57.2 (5.1)	58.4 (5.0)	59.2 (4.6)	58.9 (5.0)
BMI, mean (SD), mg/kg^2	26.3 (3.8)	24.6 (3.8)	27.1 (4.3)	26.3 (4.1)
Years of smoking, mean (SD)	35.9 (8.5)	37.9 (8.2)	37.4 (6.9)	37.1 (9.8)
Alcohol, mean (SD), g/day	18.0 (21.6)	32.3 (29.5)	14.8 (15.0)	17.2 (20.1)
Primary school education (%)	79%	86%	76%	85%
Urban residence (%)	58%	57%	44%	61%
Tooth loss (%)[5]				
None	2%	4%	0%	1%
1–5 Teeth	17%	16%	21%	10%
6–10 Teeth	14%	12%	11%	10%
11–31 Teeth	35%	37%	32%	36%
Edentulous	33%	31%	36%	43%

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Cohort; BMI = body mass index; ESCC = esophageal squamous cell carcinoma.
[1]Subjects without data on tooth loss were excluded ($n = 9$).
[2]Esophageal squamous cell carcinomas.
[3]All these tumors were adenocarcinomas that infiltrated the esophagogastric junction plus two adenocarcinomas above the junction (see Methods for a complete description of case definitions).
[4]These tumors were adenocarcinomas in the body of the stomach.
[5]The first column does not total to 100% owing to rounding.

Table II. Baseline age-adjusted mean and 95% confidence intervals for selected characteristics by tooth loss category in the ATBC Study cohort[1].

	Tooth loss category			
Characteristics	0–10 Teeth missing	10–31 Teeth missing	Edentulous	*p*-value
Number	9398	10 095	9631	
Age (years)	55.4 (55.3, 55.5)	57.0 (56.9, 57.1)	59.2 (59.1, 59.3)	<0.0001
BMI (mg/kg^2)	26.5 (26.5, 26.6)	26.3 (26.2, 26.3)	26.0 (26.0, 26.1)	<0.0001
Years of smoking (*n*)	34.6 (34.5, 34.8)	36.3 (36.1, 36.4)	36.9 (36.8, 37.1)	<0.0001
Primary school education (%)	66.3 (65.5, 67.2)	81.8 (81.1, 82.6)	88.3 (87.6, 88.9)	<0.0001
Living in city (%)	49.1 (48.0, 50.0)	41.7 (40.7, 42.6)	36.6 (35.6, 37.6)	<0.0001
Peptic or duodenal ulcer (%)	15.8 (15.0, 16.6)	16.8 (16.0, 17.4)	20.0 (19.2, 20.8)	<0.0001
Serum nutrients				
Alpha-Tocopherol[2] (μg/l)	12.4 (12.3, 12.5)	11.8 (11.7, 11.8)	11.5 (11.5, 11.6)	<0.0001
Retinol (μg/l)	601 (598, 604)	586 (583, 588)	577 (574, 579)	<0.0001
Daily dietary intake[3]				
Alcohol (g)	19.5 (19.0, 19.9)	18.2 (17.8, 18.6)	16.3 (15.8, 16.7)	<0.0001
Fruit (g)	104 (103, 106)	89 (88, 91)	90 (88, 91)	<0.0001
Vegetables (g)	132 (130, 133)	109 (107, 110)	100 (99, 102)	<0.0001
Starch (g)	148.4 (147.7, 149.1)	147.6 (147.0, 148.3)	145.2 (144.5, 145.9)	<0.0001
Sodium (g)	4.9 (4.9, 5.0)	5.0 (4.9, 5.0)	4.9 (4.9, 5.0)	0.96
Zinc (mg)	15.9 (15.8, 15.9)	15.7 (15.6, 15.7)	15.5 (15.5, 15.6)	<0.0001
Vitamin C (mg)	105.3 (104.5, 106.2)	95.8 (94.9, 96.6)	93.5 (92.6, 94.4)	<0.0001
Vitamin E (mg)	12.9 (12.8, 13.0)	12.0 (11.9, 12.1)	11.3 (11.2, 11.4)	<0.0001
Nitrite (mg)	2.2 (2.1, 2.2)	2.2 (2.2, 2.2)	2.3 (2.2, 2.3)	<0.0001
Nitrate (mg)	65.5 (64.9, 66.1)	58.8 (58.2, 59.4)	56.6 (56.0, 57.3)	<0.0001

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Cohort; BMI = body mass index.
[1]Cohort limited to subjects with complete information on tooth loss ($n = 29{,}124$).
[2]Adjusted for serum cholesterol.
[3]Adjusted for energy, except alcohol, and cohort restricted to $n = 27{,}104$ with complete dietary information; 0–10 teeth missing = 8826, 10–31 teeth missing = 10,095, edentulous = 9631.

Table III. Adjusted[1] hazard ratios and 95% confidence intervals for tooth loss and upper GI cancer at three sites in the ATBC Study cohort.

	ESCC				Esophageal/gastric cardia adenocarcinoma[2]				Gastric non-cardia adenocarcinoma[2]			
Tooth loss	N cases	HR	95% CI	*p*-value	N cases	HR	95% CI	*p*-value	N cases	HR	95% CI	*p*-value
0–10 teeth lost	16	1.00	(Reference)		21	1.00	(Reference)		37	1.00	(Reference)	
11–31 teeth lost	18	0.92	0.46, 1.83		21	0.86	0.46, 1.60		65	1.46	0.97, 2.21	
Edentulous	15	0.73	0.35, 1.55	0.69	24	0.93	0.50, 1.75	0.84	77	1.65	1.09, 2.49	0.020

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Cohort; GI = gastrointestinal; ESCC = esophageal squamous cell carcinoma; HR = hazard ratio.
[1]Adjusted for age at randomization and education.
[2]See footnotes for Table I and the Methods section for a complete description of case definitions.

Previously, the association between tooth loss and esophageal or gastric cancers has been examined in only a single prospective study, and that study showed it to be associated with increased risk of ESCC, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma [8]. In that study, the relative risks were similar among all three sites, but the highest point estimates were reported for gastric non-cardia adenocarcinoma. The reasons for the differences between that study and the current one are not known, but several differences between the Chinese cohort in the previous study and the Finnish cohort examined here have been noted. Linxian China has some of the highest rates of ESCC and gastric cardia cancer in the world [19], but Barrett's esophagus and esophageal adenocarcinoma are absent [20]. Tobacco and alcohol account for a great portion of the contributable risk for ESCC in Western populations [21] but have been shown to be of relatively minor importance in Linxian populations [22]. Similarly, risk factors for gastric cardia cancer in Linxian China may differ from those in other parts of the world. For example, *H. pylori* seropositivity is associated with an increased risk of gastric cardia cancer in Linxian, but not in Western populations [23]. For this analysis, we combined esophageal adenocarcinomas and adenocarcinomas that invaded the esophagogastric junction as a single entity because there is no clear way to separate tumors infiltrating the junction at the time of diagnosis into those arising in the esophagus and those arising in the gastric cardia [24,25]. This may have inhibited our ability to detect an association if tooth loss has distinct actions in these two tumor sites.

Several different hypotheses could explain the tooth loss and cancer association. Tooth loss could be associated with a dietary pattern that increases the risk of gastric cancer, but when we adjusted our hazard models for dietary factors we saw no evidence of confounding. Polymorphisms in certain genes that mediate inflammatory responses affect the severity of periodontal disease [26] and also modify the risk of gastric cancer [27]. Therefore, the association could be due to an individual's propensity to handle inflammation poorly rather then a specific effect of tooth loss (i.e. confounding by genetics). Poor oral hygiene has been linked to increased internal

Table IV. Adjusted odds ratios and 95% confidence intervals for tooth loss and upper GI cancer at two sites with and without adjustment for *Helicobacter pylori* seropositivity in a subset of the ATBC Study cohort.

		Esophageal/gastric cardia adenocarcinoma[2]				Gastric non-cardia adenocarcinoma[2]			
H. pylori adjustment[3]	Tooth loss	N cases[4]	OR	95% CI	*p*-value	N cases[4]	OR	95% CI	*p*-value
Without *H. pylori*	0–10 teeth lost	19	1.00	(Reference)		36	1.00	(Reference)	
	11–31 teeth lost	20	0.99	0.48, 2.06		63	1.68	1.00, 2.82	
	Edentulous	23	1.30	0.63, 2.68	0.46	75	2.18	1.28, 3.69	0.0042
With *H. pylori*	0–10 teeth lost	19	1.00	(Reference)		36	1.00	(Reference)	
	11–31 teeth lost	20	1.05	0.50, 2.19		63	1.62	0.95, 2.76	
	Edentulous	23	1.40	0.67, 2.93	0.35	75	2.09	1.22, 3.60	0.0078

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Cohort; GI = gastrointestinal; OR = odds ratio.
[1]Adjusted for age at randomization and education.
[2]See footnotes for Table I and the Methods section for a complete description of case definitions.
[3]*H. pylori* was categorized as either negative for whole cell *H. pylori* and Cag A or positive for either.
[4]Both esophageal adenocarcinomas, two junctional cancers cases, and two gastric non-cardia adenocarcinoma cases did not have serum available for *H. pylori* assessment. These cases were excluded from the logistic models.

production of nitrosamines [28], some of which are gastrointestinal organ-specific carcinogens. Poor oral hygiene and the attendant greater tooth loss might cause greater endogenous nitrosamine production and therefore greater risk of gastric cancer.

Our prospective cohort was derived from a large randomized trial with extensive information on potential confounders and complete follow-up. The reliability and validity of the dietary instrument [12] indicates that we should have good estimates of potentially confounding dietary factors and there was no evidence of confounding when we adjusted the hazard models for numerous dietary factors. Other investigators examining the tooth loss–cancer association have hypothesized that insufficient control for confounding by smoking could underlie reported associations [9]. Most previous reports have examined cancers with relatively strong associations with smoking (e.g. oral cancer, ESCC, or lung cancer), but the association between smoking and gastric cancer is weaker. Extensive analysis of potential confounding by smoking revealed no evidence that this could explain our association. The existence of other unmeasured confounders remains a possible explanation for our results.

In a prospective Finnish cohort of male smokers, tooth loss was associated with higher incidence of gastric non-cardia adenocarcinoma and this association persisted after adjustment for numerous potential confounding factors, including *H. pylori* seropositivity. In this same cohort, there was no apparent association between tooth loss and incident ESCC or esophageal/gastric cardia adenocarcinoma.

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